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Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohio community with environmental airborne manganese exposure☆

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ABSTRACT

Manganese (Mn) is a nutrient and neurotoxicant sometimes associated with mood, motor and neurological effects. Reports of health effects from occupational exposure to Mn are well known, but the reported links to environmental airborne Mn (Mn-Air) are less conclusive. Marietta, OH (USA) is a previously identified community with elevated Mn-Air from industrial emissions. Households were randomly selected in Marietta and the comparison town (Mount Vernon, OH). The responders were used to recruit on a voluntary basis 30- to 75-year-old residents, i.e. 100 in Marietta and 90 in Mount Vernon. They were administered the Unified Parkinson's Disease Rating Scale (UPDRS), motor efficiency, and mood tests, along with a comprehensive questionnaire including demographics, health and work history. Blood Mn (MnB), serum ferritin, and hepatic enzymes were measured. Results were compared with those of 90 residents from a demographically similar comparison town, Mount Vernon, OH, where Mn-Air from industrial emissions was not of concern. Mn-Air exposure indices were modeled for Marietta residents. The Mn-exposed participants resided on average 4.75 miles (range 1–11) from the Mn point source. Their modeled residential Mn-Air estimate ranged from 0.04 to 0.96 $\mu g/m^3$ and was on average 0.18 $\mu g/m^3$. The group means of MnB were similar for the Mn-exposed (9.65 μg/L) and comparison (9.48 μg/L) participants. The Marietta group reported more generalized anxiety on the Symptom Checklist-90-Revised (SCL-90-R) than the comparison group ($p = 0.035$). Generalized anxiety in Marietta was related to a cumulative exposure index ($p = 0.002$), based on modeled Mn-Air concentration and length of residence. Higher generalized anxiety scores were related to poorer performance on UPDRS tests [adjusted relative risk (95%CI): 2.18 (1.46–3.25) for motor-related activities of daily living, 3.44 (1.48–7.98) for bradykinesia, and 1.63 (1.06–2.53) for motor/movement]. Group differences in SCL-90-R generalized anxiety between the two towns and the observed relationship between exposure indices and generalized anxiety suggest an association between environmental Mn exposure and anxiety states. Whether this association is due to direct neurotoxic effects of Mn-Air or concern about the health effects of air pollution remains an open question. The results highlight the importance of measuring anxiety in relation to neuropsychological and neurological endpoints, and should be validated in other studies of Mn-exposed communities.

Introduction

Mn is found in air, dust, soil, water, and food, and is an essential dietary element. High inhalation exposure to manganese (Mn) particulates in dust and/or fumes in the workplace is a well-known risk for deteriorating psychiatric health, declining cognitive ability, and movement disorders similar to Parkinson's disease (PD) (Bowler et al., 2007a,b; Couper, 1837; Feldman, 1999). Studies on health risks in the general population suggest an association with

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Table 1
Review of adult manganese studies of mood effects.

Authors (Year)	Study population	Symptom domains of generalized anxiety[a]			Measures
		Domain I anxiety, nervousness, and irritability	Domain II emotional disturbance and lability	Domain III impulsive and compulsive behaviors	
Environmental manganese exposure studies					
Donaldson (1987)	Chilean residents	(+)	*ne*	*ne*	Symptoms
Gottschalk et al. (1991)	Prisoners	*ne*	*ne*	(+)	Symptoms
Bowler et al. (1999)	Canadian adults	(+)[b]	(+)[b]	(−)	BSI, POMS
Sassine et al. (2002)	Canadian adults	(+)[c]	(+)[c]	(+)[c]	BSI, SCL-90-R
Occupational manganese exposure studies					
Collier (1939)	Industrial workers	*ne*	(+)	(+)	Symptoms
Penalver (1955)	Miners	(+)	*ne*	(+)	Symptoms
Schuler et al. (1957)	Miners	(+)	(+)	(+)	Symptoms
Abd El Naby (1965)	Drillers, Mn ore porters	*ne*	*ne*	(+)	Symptoms
Mena et al. (1967)	Miners	(+)	(+)	(+)	Symptoms
Tanaka and Lieben (1969)	Industrial plant workers	(+)	(+)	*ne*	Symptoms
Chandra et al. (1974)	Mn mine drillers	*ne*	(+)	*ne*	Symptoms
Jonderko et al. (1979)	Ferro- and silico-Mn foundry	(+)	(+)	(+)	Symptoms
Yamada et al. (1986)	Mn ore crushing – case study	*ne*	(+)	*ne*	Symptoms
Roels et al. (1987)	Mn oxide and salt plant workers	(+)	(+)	*ne*	Symptoms
Ferraz et al. (1988)	Agricultural workers	(+)	*ne*	*ne*	Symptoms
Wang et al. (1989)	Ferro-Mn smelter workers	(+)	*ne*	*ne*	Symptoms
Sjögren et al. (1990)	Welders	*ne*	(+)	*ne*	Symptoms
Wennberg et al. (1991)	Steel smelter workers	(−)	*ne*	*ne*	CPRS, Symptoms
Reidy et al. (1992)	Migrant farm workers	(+)	*ne*	*ne*	Symptoms
Mergler et al. (1994)	Mn alloy workers	(+)	(+)	*ne*	POMS
Lucchini et al. (1999)	Ferroalloy workers	(+)	*ne*	*ne*	Symptoms
Sinczuk-Walczak et al. (2001)	Welders & battery workers	(+)	(+)	(+)	Symptoms
Racette et al. (2001)	Welders	*ne*	(+)	*ne*	Symptoms
Bouchard et al. (2003)	Ferro- & silico-Mn alloy workers	(−)	*ne*	*ne*	POMS
Bowler et al. (2003)	Welders	(+)	(+)	(+)	BSI, POMS
Myers et al. (2003)	Mn smelting production workers	(+)	*ne*	*ne*	Symptoms
Yuan et al. (2006)	Welders	(+)	*ne*	*ne*	POMS
Bowler et al. (2006a)	Welders	(+)	(+)	(+)	POMS, SCL-90-R
Bowler et al. (2006b)	Welder – case study	(+)	(+)	(+)	POMS, SCL-90-R
Bowler et al. (2007a)	Welders	(+)	(+)	(−)	SCL-90-R
Bowler et al. (2007b)	Welders	(+)	(+)	(+)	SCL-90-R
Bouchard et al. (2007a)	Ferro- & silico-Mn alloy workers	(−)	*ne*	*ne*	POMS
Bouchard et al. (2007b)	Ferro- & silico-Mn alloy workers	(+)	(−)	(−)	BSI, SCL-90-R
Chang et al. (2009)	Welders	(−)	*ne*	*ne*	POMS

[a] (+) = positive finding; (−) = negative finding; *ne* = not examined.
[b] Blood manganese and age interaction effect in men.
[c] Interaction with alcohol consumption. BSI: Brief Symptom Inventory; POMS: Profile of Mood States; SCL-90-R: Symptom Checklist 90-Revised; CPRS: Comprehensive Psychopathological Rating Scale.

environmental exposure to Mn in ambient air (Mn-Air) from a variety of industrial point or mobile sources in Canada (Finkelstein and Jerrett, 2007; Mergler et al., 1999). Using geographic analyses, Lucchini et al. (2007) reported an increased prevalence of parkinsonian disorders among residents living in the Mn-polluted vicinity of Italian ferroalloy industries. Similarly, in a nationwide analysis, a higher risk of PD diagnosis was found among U.S. Medicare beneficiaries in urban counties with industries reporting high levels of Mn releases to the environment (Willis et al., 2010). These community studies focused on movement disorders, but not on mood, with one exception (Bowler et al., 1999).

Although used as a main outcome measure in numerous studies of chemical exposures (Baum et al., 1986; Bowler et al., 1994; Gatchel et al., 1985; Green, 1991), anxiety measures rarely included standardized scales of affect and mood in Mn studies during 1939–2009 (Table 1). All 34 studies are occupational, with the exception of one prison study (Gottschalk et al., 1991) and three environmental community studies (Bowler et al., 1999; Donaldson, 1987; Sassine et al., 2002). Higher levels of self-reported symptoms or elevated scores on objectively measured tests of mood were reported in 23 studies (67.6%) for Domain I (anxiety, nervousness, and irritability), in 19 studies (55.9%) for Domain II (emotional disturbance and lability), and in 13 studies (38.2%) for Domain III (impulsive and compulsive behaviors). Twenty-one studies (61.8%) assessed symptoms of affect and mood by self-report. Clinical and empirical neurotoxicological studies more frequently apply standardized and normed scales since the 1990s (Table 1), including the Profile of Mood States (POMS) (McNair et al., 1992), the Symptom Checklist 90-Revised (SCL-90-R) (Derogatis, 1992), and the 53-item Brief Symptom Inventory (BSI) (Derogatis, 1993). Although not used for psychiatric diagnoses in itself, the SCL-90-R is used to classify generalized anxiety disorders consistently with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Derogatis, 1992).

Marietta, Washington County, OH, has experienced long-term Mn-Air emissions from Eramet Marietta, Inc. (EMI), a major U.S. ferro- and silicomanganese producer, since the early 1950s (U.S. EPA, 1984, 2010d). State activist and local community groups have long expressed health concerns over industrial Mn pollution from EMI, conducting large-scale letter writing campaigns and producing reports of environmental concerns (OCA, 2011). In addition to special air monitoring projects related to Mn emissions (ATSDR, 2009; U.S. EPA, 2010c), the Ohio EPA has operated six air monitors for emission of toxic metals and particulates at various times and locations, since 1991, as air pollution control needs have arisen (Ohio EPA, 2010).

Mount Vernon, Knox County, OH, was selected as a comparison town for its demographic similarity (U.S. Census Bureau, 2001a,b), as well as its low number of major industries (U.S. EPA, 2011b). Consequently, the Ohio EPA has no area air pollution control activities related to toxic metals and particulate emissions (Ohio EPA, 2010). In contrast to Marietta, the level of community environmental concern in Mount Vernon is low with no organized activism (OCA, 2011).

Mount Vernon was shown to differ greatly from Marietta for Mn emissions in National Air Toxics Assessments (U.S. EPA, 2010b). Although changes in methodology and reporting make direct comparisons across assessment years difficult, Mn-Air emissions for the Marietta study area were ranked among the highest in the U.S., with 99% attributed to point sources. In the Mount Vernon study area, Mn-Air emissions were slightly above background models of long-range transport and from natural emission and other unknown sources (U.S. EPA, 2009a, 2011a). In Washington County, Mn-Air emissions were ranked above the 95th U.S. percentile, while Knox County emissions were ranked below the 25th U.S. percentile (U.S. EPA, 2002, 2006).

The purpose of this study was to compare the prevalence of medical and mental health outcomes and symptoms among participants from two Ohio towns, with and without industrial Mn-Air emissions. Study objectives were: (1) to evaluate clinical and statistical differences between the towns in the distributions of generalized anxiety, motor/movement scores from the Unified Parkinson's Disease Rating Scale (UPDRS), motor efficiency scores, and symptom prevalence; (2) to investigate whether there is a relationship between Mn exposure and generalized anxiety, motor efficiency, and motor/movement functions; and (3) to examine and compare the association between generalized anxiety and UPDRS and motor efficiency between the towns.

Materials and methods

Recruitment and selection

Local public health and city administrative staff in Marietta and Mount Vernon, OH were engaged in the planning and approvals for the proposed study. News releases, a public meeting in Marietta, and an open city council meeting in Mount Vernon announced the forthcoming study.

Because Ohio has areas with naturally occurring Mn and iron (Fe) in groundwater, an *a priori* decision was made to restrict all participants to those whose homes were served by public water companies, which are required by Ohio State Code to reduce Mn and Fe levels to national secondary maximum contaminant levels. Laboratory analyses by the respective water departments confirmed that Mn and Fe in drinking water were treated as required in both towns. For Marietta participants, a random sample of parcels was drawn from December 2008 property tax records within the ZIP code 45750. In order to sample residents living closest to EMI, this mixture of rural and urban parcels were verified against water company records and were further restricted to the zone where modeled Mn-Air was 0.04 $\mu g/m^3$ or higher. For Mount Vernon, a random sample of parcels was drawn from March 2009 property tax records within the city boundary, all serviced by the city water authority.

Commercial properties were excluded from the sampling frames. Random numbers assigned to each address were sorted in ascending order; the first 300 sorted addresses were sent study recruitment letters. Additional letters were sent until a sufficient number of participants per town were recruited. For apartments, one unit was selected at random among the building units for inclusion in the address list. A pre-addressed, stamped post card was to be returned to the study team indicating interest in participation. Those who returned the card received a minimum of three follow-up telephone calls during which the eligibility screening questionnaire was administered and an appointment for testing was scheduled. Up to two participants per household were permitted.

Inclusion criteria included being aged 30–75 years and having lived in the respective town for 10 or more years. The following exclusion criteria were applied: having a diagnosed neurodegenerative disease (multiple sclerosis, Alzheimer's dementia, Huntington's chorea, PD), brain ailments (meningitis, encephalitis, stroke with hospitalization for more than one day, brain surgery, prior head injury, epilepsy), psychiatric conditions (schizophrenia, major psychiatric diagnosis, and bipolar disorder), current medical treatment (anticonvulsive, alcohol/drug dependence, and hepatic condition), pregnant or nursing, medically unable to participate in the study, exposure to hazardous chemicals other than Mn (pesticides, fungicides, herbicides, carbon monoxide, and neurotoxic metals), including ever having worked at EMI.

A total of 1732 invitation letters were mailed to randomly selected Marietta households. Of those, 264 individuals expressed interest and 122 were eligible and available for testing. In Mount Vernon, 2297 invitation letters were sent, 245 individuals expressed interest, and 117 were eligible. We refer to results for Marietta residents as 'Exposed' and those for Mt. Vernon residents as 'Comparison'. In total, 270 respondents to the random mailings were excluded based on the study's exclusion criteria, or were unable to participate. Of the 239 interested and eligible, 191 participants (Exposed: $n = 100$, Comparison: $n = 91$) from 150 households (Exposed: $n = 76$, Comparison: $n = 74$) were recruited on a voluntary basis and tested. On the basis of the study design, it was decided *a priori* that a total number of only 200 participants would be examined, i.e. 100 in Marietta and 100 in Mount Vernon. In Marietta all scheduled residents came to their appointment, while in Mount Vernon 9 residents did not show up for reasons of personal inconvenience. One participant from the comparison town was excluded post-testing due to insufficient length of residency, leaving 100 Mn-exposed and 90 comparison participants for analyses. For an eligible resident, an appointment was set for testing day and time. A reminder call was given within 48 h of the appointment time and day. Each participant who completed the study was given a $50 gift card. The length of the appointment for each participant lasted between 2½ and 3 h.

The Ohio Department of Health (ODH), the U.S. and Ohio Environmental Protection Agencies (EPAs), and the Agency for Toxic Substances and Disease Registry (ATSDR) provided technical assistance, study design input, and review of the San Francisco State University (SFSU) protocol. The institutional review boards of SFSU and the ODH granted research approval. Written informed consent was obtained and data collection occurred during August, 2009.

Measures

Questionnaire

During the appointment, a self-administered questionnaire captured information on length of residence, medical history and symptoms, current medications, medical or mental health diagnoses, work history, job category, past chemical exposures, hobbies, lifestyle behaviors, time spent indoors and outdoors, perceived local pollution, dietary and supplement intake of Mn and Fe, and demographics. The medical symptoms questionnaire (MSQ) comprised 76 items on parkinsonian and general medical symptoms. It included the following categories: neurologic, musculoskeletal, motor, memory/concentration, anxiety, depression, sleep disorder, headache/chemical sensitivity, visual, sensory, dermatological, gastro-intestinal, and respiratory problems. The MSQ was developed with input from movement disorder neurologists, internal medicine specialists, neurotoxicologists, and neuropsychologists. A similar medical questionnaire was previously used for Mn-exposed welders (Bowler et al., 2007a,b).

Standardized test battery

The test battery included tests of mood, motor/movement function, motor efficiency, and mental effort. The mood tests comprised: (1) the *Symptom Checklist-90-Revised (SCL-90-R)* (Derogatis, 1992); (2) the *Environmental Worry Scale (EWS)* (Bowler and Schwarzer, 1991); and (3) the *Health-Related Quality of Life (HRQOL) Scale* (CDC, 2008). Derogatis (1992) describes a generalized anxiety syndrome characterized by elevations on the Anxiety, Obsessive/Compulsive and Phobic Anxiety dimensions of the SCL-90-R. A summary generalized anxiety scale was constructed by computing the arithmetic mean of the sex-adjusted SCL-90-R T scores of the three dimension scales.

The functional motor/movement tests consisted of two components from the *Unified Parkinson's Disease Rating Scale (UPDRS)* (Goetz et al., 2003): (1) Part II [motor-related activities of daily living (ADL)]; and (2) Part III (motor/movement examination). The UPDRS was administered by an occupational physician (YK) specialized in assessing Mn-exposed workers. Standardized motor efficiency tests were administered by trained psychometricians under the supervision of the principal investigator and neuropsychologist (RMB) and a senior neuropsychologist (SR). They included the following tests: (1) *Fingertapping* (Lezak et al., 2004); (2) *Grooved Pegboard* (Lezak et al., 2004); and (3) *Grip Strength (Dynamometer)* (Lezak et al., 2004).

The *Similarities subtest* from the Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III), assessing higher level verbal abstraction, was also administered as a test of premorbid intellectual function (Wechsler, 1997).

Tests of mental effort were administered: (1) the *Rey 15-Item Test* (Lezak et al., 2004) and (2) *Victoria Symptom Validity Test* (Slick et al., 1997). Sufficient effort was based on scoring criteria 9 or above on the Rey 15 Item Test or in the "valid" range on the Victoria Symptom Validity Test.

All remaining tests were scored according to their respective test manuals. The motor efficiency tests were scored with the Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery (HRB), adjusting for age, ethnicity/race, sex, and education (Heaton et al., 2004), and were expressed as T scores. The UPDRS Parts II and III were scored according to the recommended methods of the Movement Disorder Society Task Force (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). Test protocols were double-scored and discrepancies were resolved by the principal investigator or a senior staff member. Double data entry was used. Scoring and data entry of all tests were performed blinded to exposure status to assist in controlling scorer bias; participant identification numbers for both towns were interspersed.

Biomarkers

Certified phlebotomists drew blood samples from each participant. Serum samples were frozen during storage and shipment, and were analyzed at U.S. EPA's Analytical Chemistry Core (Research Triangle Park, NC) for ferritin as a biomarker of Fe status and for two hepatic enzymes, alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT). Abnormal values of these biomarkers may indicate compromised Mn homeostasis.

Whole blood samples were cooled during storage and shipment, and were analyzed at the CDC's National Center for Environmental Health Laboratory (Atlanta, GA). Whole blood was tested for Mn, Hg, Pb, and Cd concentrations using a multi-element analytical technique by quadrupole inductively coupled plasma mass spectrometry in combination with the dynamic reaction/collision cell mode (ICP-DRC-MS) (CLIA method: Centers for Disease Control and Prevention/Division of Laboratory Science, 2003, 2009). The blood sample was diluted twice with 18 MΩ water and then another 25 times with 18 MΩ water-based diluents containing 1% (v/v) tetramethylammonium hydroxide, 0.05% disodium ethylenediamine tetraacetate, 0.05% Triton X-100, and ethyl alcohol at 10% for Mn or 5% for Hg, Pb, and Cd. Gold was added to reduce intrinsic Hg memory effects. For internal standardization rhodium was added for Mn and Cd, and bismuth for Hg and Pb analyses (Barany et al., 1997; Date and Gray, 1989; Delvis, 1999; Nixon et al., 1999).

Estimating environmental Mn exposure (Marietta only)

Dispersion modeling was conducted using the AERMOD modeling system for the Marietta study area (U.S. EPA, 2009b). Model inputs included 2001 Mn air emission data, terrain data, and 1991–1995 surface and upper air meteorological data from the Parkersburg, WV, airport and Dayton, OH, weather service stations, respectively (NOAA, 2010; USGS, 2010; WebMET, 2010). A geographic information system grid overlay was created to map the Mn-Air dispersion in the study area. Manganese concentrations, in $\mu g/m^3$, were averaged over the five-year meteorological period of 1991–1995, rather than more recent years "due to a change in the way data was collected" (U.S. EPA, 2010a), for each $10\,m \times 10\,m$ grid cell using its centroid as a proxy receptor for actual residences located therein. Air dispersion modeling for Mn concentrations in Mount Vernon was not conducted given its lack of large industries (U.S. EPA, 2010d).

A cumulative exposure index (CEI) for Mn-Air was calculated for each participant in Marietta, which was the product of the modeled Mn air concentration of the assigned receptor site and the length of time the participant resided in Marietta. This index was not a measure of personal exposure, but rather was used to estimate a participant's potential magnitude for environmental exposure to Mn-Air relative to other participants in the sample.

Statistical analysis

Demographics, biomarkers, and exposure indices were compared between the two towns using the mean, standard deviation, median and range, and *p*-values from the independent-samples *t*-test or nonparametric test for continuous variables. The frequencies for each level of the categorical variables and *p*-values from the Fisher's exact test were reported.

Age-adjusted Similarities test scores from the WAIS-III were compared between participants from both towns with a between-groups analysis of covariance (ANCOVA), controlling for education level, sex, and use of psychiatric health medications.

SCL-90-R generalized anxiety, motor efficiency, and UPDRS scores were compared between the two towns using between-subjects comparisons by independent-sample *t*-tests, Mann–Whitney *U* test, and ANCOVA. Cohen's effect size (Cohen, 1988) and the percentile of the mean generalized anxiety T score were also reported for each town. Multiple regression models were performed with effect variables and MnB.

In the Marietta group, multiple regression models were also performed with effect variables and CEI. For these analyses, natural logarithmically transformed CEI values (ln CEI) were use, as the distribution of non-transformed values had high levels of skewness, kurtosis, and outliers. Additionally, the generalized anxiety score was compared between the lowest and the highest CEI quartile within the exposed town. The demographic characteristics and generalized anxiety score among participants in the lowest CEI quartile of the exposed town were compared to those of the comparison town participants.

To assess the association between the generalized anxiety score, motor efficiency tests, and UPDRS scores, spline smoothing functions were used to detect underlying linear or nonlinear associations between the generalized anxiety and continuous outcomes of motor efficiency tests (Fingertapping of dominant and nondominant hand) and UPDRS scores [activities of daily living (ADL), bradykinesia, motor]. Based on the smoothing functions, clinical judgment, and to facilitate interpretation of the association in terms of risk, the five outcome variables and the generalized anxiety score were dichotomized. A generalized anxiety T score greater than 55 was considered "high", indicating more anxiety. A Fingertapping T score less than 45 was considered "impaired". Activities of daily living, bradykinesia, and motor scores greater than zero were considered "impaired" or worse performance.

The crude prevalence of impairment on motor efficiency tests (Fingertapping of dominant and nondominant hand) and UPDRS scores [activities of daily living (ADL), bradykinesia, motor] exceeded 10%; therefore, the generalized linear model with log link and Poisson error distribution was used to estimate the adjusted relative risk, rather than the logistic regression model (Zou, 2004). The following covariates were considered: age, sex, diabetes, education, health insurance status, and psychiatric medication. Only health insurance status was used as a confounding covariate in the final model for Fingertapping scores which were already normalized for age, sex, and education. For the three UPDRS outcomes, age, sex, and health insurance were used as confounding covariates in the models. Analyses were performed with Predictive Analytics Software (PASW 18.0) (SPSS Inc., 2009), and SAS/STAT software (SAS Institute Inc., 2003).

Results

Demographics, biomarkers, and indices of environmental Mn exposure

Table 2 compares the demographic characteristics of the Marietta and Mount Vernon study groups. The Mn-exposed and comparison participants were highly similar in age, sex, educational attainment, years of residence, smoking, alcohol consumption, the percent of people within each annual household income category, and work history. In addition, both groups were predominantly Caucasians (Exposed: 94%, Comparison: 96.7%). The study groups did not differ on marital status (Exposed: 81% married, Comparison: 76% married), obesity (i.e. body mass index > 30 kg/m^2) (Exposed: 40%, Comparison: 50%) or proportion of uninsured participants (Exposed: 12%, Comparison: 19%). The participants in Marietta resided on average 4.75 miles (range: 0.99–11.00) from the Mn point source. Their modeled residential Mn-Air estimate ranged from 0.04 to 0.96 μg/m^3 and was on average 0.18 μg/m^3, and the mean CEI was 6.67 μg/m^3 $\times$ years (range: 0.89–41.22) (Table 2).

The average concentrations of MnB did not differ between both towns (Exposed: 9.65 μg/L, Comparison: 9.48 μg/L) and were within other general population reporting of 4–15 μg/L (ATSDR, 2008). There were few MnB values above the upper range (Exposed: $n = 6$, Comparison: $n = 7$); none were related to low serum ferritin (Exposed: $n = 2$, Comparison: $n = 2$). On the whole, the hepatic enzymes were normal. However, a few elevated exceptions were noted; these were unrelated to abnormal MnB concentrations [ALT (Exposed: $n = 1$, Comparison: $n = 1$); GGT (Exposed: $n = 2$; Comparison: $n = 3$)]. The biomarkers of exposure to other neurotoxic metals showed no difference between the Marietta and Mount Vernon groups (Table 2).

Group comparisons and descriptive statistics of health outcomes

All participants in the study exhibited sufficient test effort (data not shown). Scores on the UPDRS, motor efficiency tests, and the SCL-90-R generalized anxiety scale were compared between the two towns (Table 3). The generalized anxiety T scores in Marietta and Mount Vernon had similar ranges, but the Mn-exposed participants showed a slightly higher average T score (mean ± SD, 54.1 ± 9.0) than comparison participants (mean ± SD, 51.6 ± 7.0) ($p = 0.035$) with an effect size of 0.308. This is considered a small to medium effect size (Cohen, 1988).

After application of the HRB adjustments for age, sex, ethnicity, and education, the standardized motor efficiency test scores also showed that the two study groups performed similarly (Table 3); the group means and standard deviations were within the average range of the normative data. Scores on two of the UPDRS scales differed; the exposed group had higher levels of bradykinesia ($p = 0.04$) and motor disturbance ($p = 0.034$). However, these effect sizes were small (0.196 and 0.222).

Age-adjusted Similarities test scores from the WAIS-III were compared between participants from both towns with a between-groups ANCOVA, controlling for education level, sex, and use of psychiatric health medications. No significant difference was found ($p = 0.915$) between mean scores of those in the exposed group (10.8 ± 3.1) and those in the comparison group (11.2 ± 2.7). Scores in both towns were very close to (although slightly higher than) those found in the general population (scaled score = 10).

Table 4 compares the prevalence of significant symptoms from the MSQ between the two towns. The exposed group was more likely than the comparison residents to report symptoms of emotional instability (feeling anxious and irritable, personality changes), autonomic nervous system symptoms (excessive perspiration, chills and fever, and nausea), sensory dysfunction (smell and taste changes), chemical sensitivity and frequent headaches, and tightness of facial muscles (possibly indicative of parkinsonism).

Comparison of health outcomes related to mood and quality of life showed no differences for the HRQOL percent of participants reporting poor or fair health (Exposed: 17%, Comparison: 10%), or the average number of days per month of poor physical (Exposed: 5.4 days, Comparison: 4.2 days) or mental health (Exposed: 5 days, Comparison: 4.2 days). The exposed and comparison participants also scored similarly on the EWS (mean and SD, Exposed: 9.45 ± 2.98; Comparison: 9.37 ± 3.00). However, when asked in a brief interview by the PI about perceived pollution in their town, 73.0% of participants ($n = 54$) in the exposed town indicated that they believed their town was polluted, while only 20.9% ($n = 18$) from the comparison town sample believed their town was polluted ($p < 0.001$).

Within the exposed town, the first quartile of the CEI had a similar distribution of generalized anxiety scores as those of the comparison town (Fig. 1). The comparison of generalized anxiety scores between the first quartile CEI and the fourth quartile CEI within the exposed town accounts for reporting bias and showed a statistically significant difference ($p = 0.004$), and a large effect size (0.82). No covariates were included in this model as the lowest and highest quartiles did not differ on age, education, income, sex, psychiatric health medication intake, health insurance status, or diabetes.

In multiple regression models controlling for age, sex, education, diabetes, mental health medication, and health insurance status, generalized anxiety T scores significantly associated with ln CEI ($b = 3.42$; $p = 0.002$) in the exposed group. When distance of residence and ln CEI were included as predictors of generalized anxiety, neither ln CEI nor distance of residence were significant predictors, as almost equal proportions of variance in generalized anxiety are explained by ln CEI ($sr^2 = 0.040$) and residence distance from EMI ($sr^2 = 0.036$) individually. Similar multiple regression models controlling for an additional covariate, musculo-skeletal illness, did not show significant associations between ln CEI and Fingertapping, Dynamometer, Grooved Pegboard T scores, the UPDRS scale

Table 2
Demographics, biomarkers, and air manganese exposure indices (for Marietta only), by study group.

Characteristics	Marietta (Exposed) $N = 100$				Mount Vernon (Comparison) $N = 90$				p-Value
	n	Mean ± SD	Median	Range	n	Mean ± SD	Median	Range	
Demographics									
Age	100	54.4 ± 9.9	55.5	30.0–74.0	90	55.5 ± 11.0	55.5	32.0–75.0	0.462
Years of education	100	14.6 ± 2.7	14.0	8.0–22.0	90	15.2 ± 3.0	14.0	12.0–22.0	0.130
Years in residence	100	36.1 ± 15.8	37.0	10.0–65.0	90	33.6 ± 17.2	31.0	10.0–74.0	0.291
Sex									0.939
Male	45				40				
Female	55				50				
Current smoker	20				18				1.000
Weekly alcohol consumption, g	94	31.7 ± 63.9	0.0	0.0–392.4	85	29.2 ± 61.6	0.0	0.0–362.1	0.786
Annual household income									0.745
$0–29,999	26				14				
$30,000–59,999	28				32				
$60,000–89,999	19				19				
$90,000 and above	19				19				
Missing	8				6				
Work history									0.078
Employed	63				61				
Unemployed or retired	31				28				
Disabled	6				0				
Missing	0				1				
Biomarkers									
Blood manganese, μg/L	100	9.65 ± 3.21	9.15	4.91–24.60	90	9.48 ± 3.16	8.79	3.75–18.90	0.702
Male	45	8.80 ± 1.90	8.60	5.10–12.50	40	9.20 ± 3.20	8.50	5.21–18.72	0.524
Female	55	10.32 ± 3.93	9.49	4.94–24.58	50	9.71 ± 3.09	9.26	3.77–18.92	0.361
Blood cadmium, μg/L	100	0.53 ± 0.53	0.31	0.14–2.87	90	0.47 ± 0.54	0.30	0.00–4.06	0.455
Blood mercury, μg/L	100	1.38 ± 1.89	0.77	0.23–14.60	90	0.96 ± 1.26	0.66	0.23–9.75	0.078
Blood lead, μg/L	100	15.6 ± 9.5	13.0	3.2–53.9	90	14.1 ± 9.5	11.4	3.1–59.6	0.277
Serum ferritin, μg/L	100	132.2 ± 153.3	76.3	12.2–858	90	130.6 ± 111.2	89.9	7.7–554	0.941
Male	45	189.6 ± 180. 3	129.0	14.3–858	40	179.4 ± 131.2	141.5	7.7–554	0.770
Female	55	85.2 ± 107.5	62.5	12.2–639	50	91.7 ± 72.7	64.5	95–329	0.722
Exposure indices									
Distance from point source, miles	100	4.75 ± 1.64	4.50	0.99–11.00					
Modeled air Mn (Mn-Air), μg/m^3	100	0.18 ± 0.13	0.16	0.04–0.96					
Cumulative exposure index (CEI)[a]	100	6.67 ± 5.9	5.53	0.89–41.22					

[a] CEI = Mn-Air × years in residence, μg Mn/m^3 × year.

scores, and the number of BRFSS-HRQOL poor mental health days per month.

When using ln MnB as a predictor of Mn exposure in similar multiple regression models with serum ferritin as an additional covariate, it was shown that it did not predict any motor outcomes either in the exposed or in the comparison group.

Association between generalized anxiety and UPDRS and motor efficiency

The relationship between generalized anxiety scores with motor efficiency and UPDRS scores, as continuous variables, was first assessed using smoothing functions to detect potential nonlinear

Table 3
SCL-90-R anxiety, motor efficiency test, and UPDRS scores, by study group.

Characteristics	Marietta (Exposed) $N = 100$				Mount Vernon (Comparison) $N = 90$				p-Value	Effect size
	n	Mean ± SD	Median	Range	n	Mean ± SD	Median	Range		
Symptoms Checklist 90-Revised										
Generalized anxiety T score[a]	100	54.1 ± 9.0	53.5	41.7–77.7	90	51.6 ± 7.0	50.5	39.3–74.7	**0.035**	0.308
Generalized anxiety percentile score		67				54				
Neuropsychological tests										
WAIS III Similarities scaled score	100	10.8 ± 3.1	11.0	4.0–18.0	90	11.2 ± 2.7	11.0	5.0–19.0	0.915	0.238
Motor efficiency tests[b]										
Fingertapping DH T-score	100	47.9 ± 11.0	48.0	21.0–71.0	90	47.5 ± 12.8	48.0	14.0–84.0	0.837	0.034
Fingertapping NDH T-score	100	46.4 ± 9.4	47.0	26.0–67.0	90	46.6 ± 11.8	46.5	19.0–78.0	0.914	0.019
Dynamometer DH T-score	100	36.6 ± 8.6	35.5	9.0–68.0	90	34.4 ± 9.8	36.0	9.0–53.0	0.113	0.240
Dynamometer NDH T-score	100	37.9 ± 8.9	36.0	21.0–73.0	90	36.8 ± 9.7	37.5	9.0–63.0	0.386	0.118
Grooved Pegboard DH T-score	100	49.9 ± 9.8	50.0	25.0–79.0	90	51.7 ± 9.9	52.5	31.0–72.0	0.191	0.183
Grooved Pegboard NDH T-score	100	48.8 ± 10.3	49.0	23.0–76.0	90	50.3 ± 10.0	51.0	29.0–77.0	0.309	0.148
Unified Parkinson's disease rating subscales[e]										
Activities of daily living (ADL)[c]	99	2.0 ± 3.1	1.0	0.0–17.0	90	1.7 ± 2.6	1.0	0.0–14.0	0.831	0.104
Body bradykinesia[d]	99	0.8 ± 2.3	0.0	0.0–13.0	90	0.4 ± 1.7	0.0	0.0–13.0	**0.048**	0.196
Motor[d]	99	1.5 ± 3.1	0.0	0.0–16.0	90	0.9 ± 2.2	0.0	0.0–13.0	**0.034**	0.222

[a] SCL-90-R generalized anxiety syndrome score = Sum of T-scores for obsessive-compulsive, anxiety, and phobic anxiety scales.
[b] DH – dominant hand; NDH – non-dominant hand.
[c] UPDRS assessment: by interview.
[d] UPDRS assessment: by physical examination.
[e] Mann–Whitney U test.

Table 4
Selected medical symptoms questionnaire results, by study group.

MSQ symptoms self-reported	Marietta (Exposed) $N=100$ No. (%)	Mount Vernon (Comparison) $N=90$ No. (%)	Unadjusted relative risk	p-Value[a]
Changes in sense of smell	14 (14.0)	4 (4.4)	3.18	0.03
Changes in sense of taste	10 (10.0)	0 (0.0)	10.0	0.002
Tightness of facial muscles[b]	8 (8.1)	1 (1.1)	7.36	0.04
Headaches > 2 per week	24 (24.0)	10 (11.1)	2.16	0.02
Headaches in the presence of gas[b]	13 (13.1)	4 (4.4)	2.98	0.04
Headaches in the presence of paint	22 (22.0)	5 (5.6)	3.93	0.001
Feeling anxious	34 (34.0)	18 (20.0)	1.70	0.04
Feeling irritable	39 (39.0)	16 (17.8)	2.19	0.001
Changes in personality	14 (14.0)	2 (2.2)	6.36	0.003
Excessive perspiration	17 (17.0)	5 (5.6)	3.04	0.02
Chills and fever	10 (10.0)	0 (0.0)	10.0	0.002
Nausea	12 (12.0)	3 (3.3)	3.64	0.03

[a] Fisher's exact test.
[b] $N=1$ missing data in exposure group.

associations (Fig. 2a–e). The smoothing curves show in general a flat line for Fingertapping and the UPDRS scores in the comparison town. For the exposure town, the smoothing curves had a negative slope for Fingertapping, where increasing anxiety is associated with decreasing motor efficiency. The exposure town had a positive slope for the three UPDRS outcomes, where increasing anxiety is associated with increasingly worse UPDRS performance.

The Fingertapping scores were dichotomized and 40% had worse function for the dominant hand, and 46% had worse function for the nondominant hand. For the three UPDRS variables, the crude prevalence of impairment ranged from 19% to 53%. There was no statistically significant association detected between generalized anxiety and the two Fingertapping tests in both towns (Table 5). All three UPDRS scales showed significant associations with generalized anxiety for the exposed town, with point estimates of the adjusted relative risks ranging from 1.63 to 3.44. For ADL, the comparison town also showed a statistically significant relative risk (1.81, 95%CI: 1.27–2.58). A model with the interaction term between town and generalized anxiety score showed that the two relative risks (Exposed: 2.18; Comparison: 1.81) were not significantly different.

Discussion

Residents of two Ohio towns were compared for potential exposure to and effects from Mn-Air. Air dispersion modeling indicated that within a 5-mile radius around the point emission source, EMI, Mn-Air concentrations in Marietta ranged from 0.04 to 0.96 μg Mn/m^3 with a mean of 0.18 μg Mn/m^3, which is about 4 times higher than the current environmental guideline values of ATSDR MRL 0.04 μg Mn/m^3 (ATSDR, 2000) and US-EPA RfC 0.05 μg Mn/m^3 (U.S. EPA, 1993). By comparison, an 8-h time-weighted average for permissible occupational exposure to inhalable Mn particulate is recommended at 200 μg Mn/m^3 (ACGIH, 1995; EU-SCOEL, 2009). For respirable particulate, 20 μg Mn/m^3 [intended change (ACGIH, 2009)] and 50 μg Mn/m^3 (EU-SCOEL, 2009) are proposed. Hence, in the early 2000s, the average residential airborne Mn exposures in Marietta may have been about two orders of magnitude lower than occupational Mn exposure limits for respirable particulate.

That MnB did not differ between the Mn-exposed and comparison residents suggests that MnB may not be an adequate indicator of Mn exposure for low-level long-term airborne Mn exposure. Recent PBPK-model results (Andersen et al., 2010; Schroeter et al., 2011) and a toxicokinetic study in welders (Hoet et al., 2011) indicate that homeostatic processes are likely to cope well with exposure to respirable Mn in concentrations below 10–20 μg/m^3. Furthermore, the PBPK model did not show any increase in accumulation of Mn in brain regions (basal ganglia) with high affinity for Mn when chronic exposures to respirable Mn particulate remain below 10 μg Mn/m^3. The similarity in MnB between the Marietta and Mount Vernon participants suggests that Mn-Air in Marietta has been too low in recent years to overwhelm the homeostatic

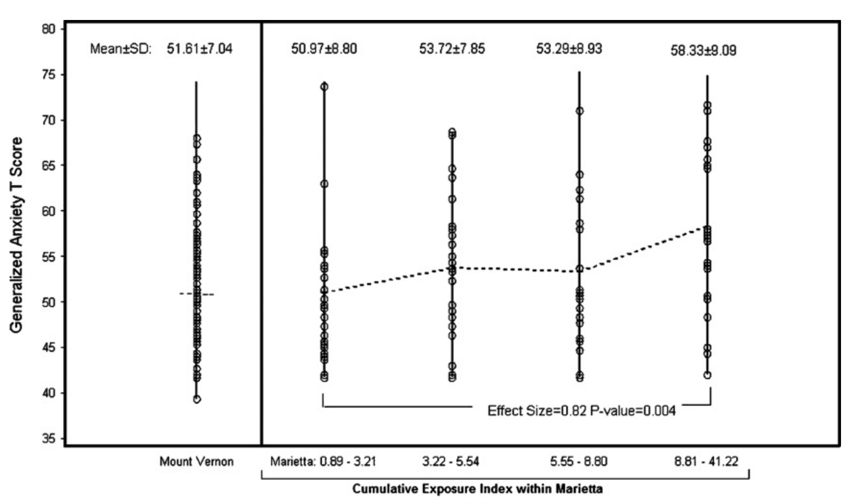

Fig. 1. Generalized anxiety T scores among quartiles of cumulative exposure index (CEI) within Marietta, and comparison with Mount Vernon generalized anxiety T scores [Mount Vernon CEIs were not computed due to lack of air monitoring and air dispersion modeling estimates (see Section "Materials and methods")].

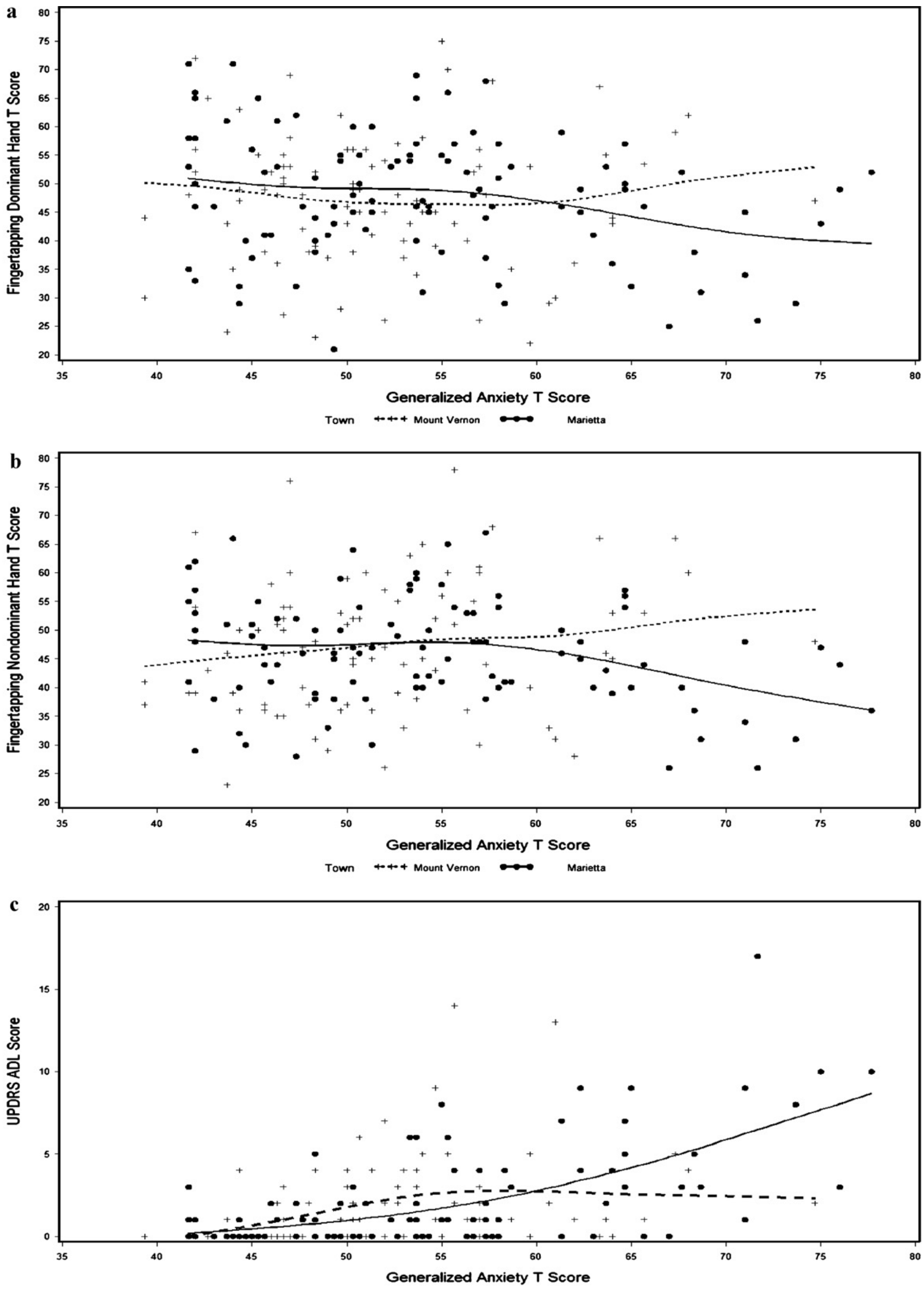

Fig. 2. (a–e) Smoothing splines of the association between generalized anxiety T scores and motor efficiency and UPDRS scores.

regulatory mechanisms of Mn which would result in increased Mn accumulation in the brain. In line with this is the lack of clear-cut differences in neurotoxic effects between Mn-exposed and comparison participants in the current study and the lack of significant associations in the exposed group between neurological endpoints (UPDRS, motor efficiency) and indices of Mn exposure (CEI, MnB). Only generalized anxiety T scores were found to be significantly associated with ln CEI, but not with ln MnB in the exposed group. When forcing distance of residence from the point source into the model, the significant association did not stand, as nearly equal

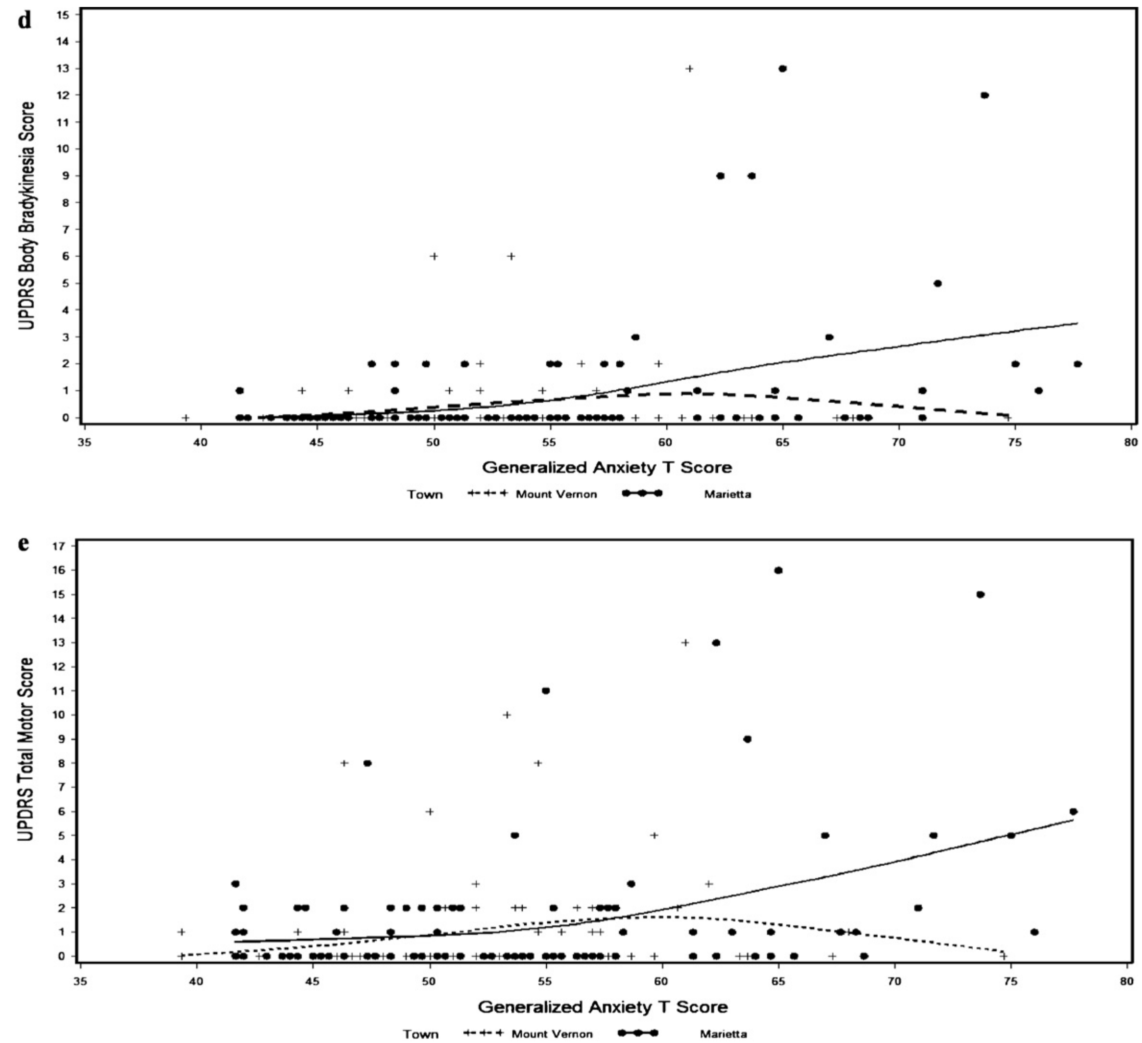

Fig. 2. (*continued*)

proportions of the variance in generalized anxiety are explained by ln CEI and distance of residence from EMI. This indicates that increased generalized anxiety in the Marietta group is most likely not linked to chronic environmental exposure to Mn-Air alone.

Our Marietta findings are at variance with those of Standridge et al. (2008) and Haynes et al. (2010). The latter authors used an US-EPA air dispersion modeling software AERMOD released in 2006 to estimate the residential Mn exposure. They reported that the estimated annual average Mn-Air concentrations in the Marietta study area varied from 0.02 to 2.61 $\mu g/m^3$, which is about double the estimate in our study (0.04–0.96 $\mu g/m^3$). However, their reported group mean Mn-Air level was 0.13 $\mu g/m^3$ which is lower

Table 5
Associations between generalized anxiety T-scores and selected motor efficiency and UPDRS scores, by study group.[a]

Dichotomized outcome variables	Overall prevalence (%)	Marietta (Exposed) $N = 100$				Mount Vernon (Comparison) $N = 90$			
		Adjusted relative risk	95%CI		*p*-Value	Adjusted relative risk	95%CI		*p*-Value
			Lower	Upper			Lower	Upper	
Motor efficiency tests[b]									
Fingertapping DH T-score <45	40	0.97	0.60	1.56	0.900	0.99	0.58	1.71	0.994
Fingertapping NDH T-score <45	46	1.23	0.79	1.90	0.353	0.88	0.52	1.49	0.635
Unified Parkinson's disease rating subscales									
Activities of daily living (ADL)[c] > 0	53	2.18	1.46	3.25	**<0.001**[e]	1.81	1.27	2.58	**0.001**[e]
Body bradykinesia[d] > 0	19	3.44	1.48	7.98	**0.004**	1.11	0.31	3.93	0.869
Other motor examination[d] > 0	35	1.63	1.06	2.53	**0.027**	1.50	0.77	2.93	0.235

[a] Generalized linear model with log link and Poisson error and robust sandwich estimator, controlling for health insurance status in the models for Fingertapping, and controlling for age, sex, health insurance status in the models for the three UPDRS outcomes.
[b] DH – dominant hand; NDH – non-dominant hand.
[c] UPDRS assessment: by interview.
[d] UPDRS assessment: by physical examination.
[e] *p*-Value for the difference in the effects of Generalized Anxiety Score between towns is 0.370.

than the mean (0.18 μg/m^3) or median (0.16 μg/m^3) value for our Marietta group. The Haynes et al. (2010) pilot study sample consisted of 141 self-identified residents who were recruited via newspaper, advertisements, fliers and direct mailing. Residents from another non Mn-exposed town were not included in their study for comparison of the biomarkers of exposure, i.e. Mn in whole blood and Mn in hair. They reported a rather weak relationship ($r = 0.30$, $n = 73$) between blood and hair Mn, however, the significance of these biomarkers as to Mn exposure still needs further clarification. It is interesting to note that the mean (range) of MnB in the Haynes et al. (2010) study, i.e. 9.12 μg/L (1.8–22), is similar to our current observations. The report of Standridge et al. (2008) deals with a small convenience sample of 22 non-randomly selected Marietta residents who participated in a community survey distributed by an activist group who had concerns over their Mn exposure. The researchers used estimates of exposure in ambient air based on an ATSDR pilot study (ATSDR, 2007), showing mean daily ambient Mn-Air exposure surrounding EMI ranging from 0.10 to 2.0 μg/m^3.

Mood effects and motor deficits are among the earliest signs of occupational Mn intoxication. Among mood effects, anxiety, nervousness and irritability have often been reported (Chandra, 1983; Donaldson, 1987; Ferraz et al., 1988; Jonderko et al., 1979; Mena et al., 1967; Mergler et al., 1994; Penalver, 1955; Reidy et al., 1992; Roels et al., 1987; Schuler et al., 1957; Wennberg et al., 1991). The present study focused on mood, motor/movement function (UPDRS), and motor efficiency in relation to chronic low-level environmental Mn exposure in Marietta residents, who have a long history of concerns about Mn-Air pollution. A cross-sectional study design, contrasting Mn-exposed and comparison groups of healthy residents, was used. The group comparison between the Mn-exposed Marietta and well-matched Mount Vernon participants revealed significantly worse scores for the Marietta group on generalized anxiety and UPDRS (motor and bradykinesia), but not on motor efficiency. The standardized effect size of 0.308 for generalized anxiety indicated a medium effect size difference between the two towns. In terms of percentile standing of the mean score (Exposed: 67th, Comparison: 54th), the difference indicates a clinically relevant effect. The quartile analysis results indicated that differences in generalized anxiety scores between the comparison group and the most exposed quartile group of residents of the exposed town is not due to a potential reporting bias in the exposed town. The highly significant large effect size of 0.82 indicated that it is this group of the most highly exposed subjects (the fourth quartile with cumulative exposure index above 8.80 μg Mn/m^3 $\times$ year) that a future study design could focus on.

Having established that for generalized anxiety scores there was indeed a medium effect size difference between the two towns, and a large effect size difference between the least exposed and most exposed groups within Marietta, the next question to address was whether the difference in generalized anxiety affected the UPDRS and motor efficiency outcomes or was associated with them. The graphs of the smoothing functions showed that for the comparison residents, there was little or no association; whereas, for the exposed town, there was a nonlinear association showing a flat slope (no association) for low level of generalized anxiety T score (below 55), and a linear association for generalized anxiety T score above 55 (higher anxiety scores were associated with worse performance). The results of the modeling show that being in the high category of generalized anxiety increases the risk of impairment or worse performance for all three UPDRS outcomes, especially for bradykinesia. Whether these associations are causally related to Mn exposure in Marietta or the result of anxiety from the fear of harmful air pollution remains an open question. Anxiety itself is likely a ‘normal’ human response to the fear and ensuing stress of observing plumes of smoke or encountering smells from smelter operations of the nearby EMI plant and other industries at the former Union Carbide site over many years. These findings emphasize that environmental studies of industrial Mn pollution should include standardized and well-normed anxiety measures.

The SCL-90-R generalized anxiety scale is considered helpful for clinicians in assessing anxiety and assigning a clinically symptomatic diagnosis of a generalized anxiety syndrome, as shown by Pedersen and Karterud (2004). Lezak et al. (2004) suggested a relationship of anxiety with neuropsychological function “after stressful and anxiety-producing life changes in work and living situations” and discussed how negative expectations about one’s abilities can affect test performance. The UPDRS and motor efficiency smoothing curve outcomes of the Marietta group are in line with Lezak’s et al. (2004) findings. In addition, in the Marietta group the prevalence of self-reported symptoms was significantly higher than in the Mount Vernon residents, including feeling anxious and irritable, and changes in personality.

At this stage it is not yet possible to discern whether increased generalized anxiety in Marietta residents reflects a direct neurotoxic effect of environmental airborne Mn exposure or whether it is related to the perception that the overall air pollution at Marietta might represent a health hazard. Anxiety about chronic chemical pollution is a common subjective reaction in communities facing industrial nuisance and visible smoke clouds from factories (Moss and Sills, 1981). Although the emissions from Marietta’s former Union Carbide industrial site (now EMI) have decreased over time, our results demonstrate anxiety that has persisted in Marietta residents. Obvious chemical spills and accidents usually generate acute reactions of anxiety in residents, while in chronic low-level exposure scenarios anxiety reactions are likely to develop more slowly and insidiously and may last for a longer period of time. Accordingly, the scores on the SCL-90-R scales for the Marietta residents overall are higher than in the comparison residents, but were still considerably lower than those reported after acute chemical events or in occupational studies (Bowler et al., 2007b).

Limitations and strengths

Mn-Air monitoring data were available for Marietta but not for Mount Vernon. Mount Vernon’s appropriateness for comparison with Marietta was based on demographic similarities, a lack of large industries emitting Mn-Air, as well as low estimates of Mn emissions (U.S. EPA, 2002, 2006, 2009a, 2010d, 2011a). The absence of air monitoring data for the comparison town is largely due to two factors: (1) the high expense of meaningful air monitoring vs. the limited budget of the present work, and (2) Mount Vernon’s appropriateness as a comparison town precludes the likelihood of air pollutant monitoring (nearly all of which is done by the State of Ohio) being conducted there. A central reason Mount Vernon was chosen is that it is demographically similar to Marietta but without a major airborne Mn source. Mount Vernon’s much lower level of industrial activity eliminates it as a place where air monitoring would be conducted, given scarce State of Ohio monitoring resources. As stated in Ohio EPA (2010), “Ohio EPA follows the Federal general guidance for air monitoring according to 40 CFR 58 Appendix D to monitor in areas of (1) expected high concentrations, (2) areas of high population density, (3) areas with significant sources, (4) general background concentration sites, and (5) areas of regional transport of a pollutant. Not all areas of the state have sites for all of these categories.”

It would have been optimal to have Mn-Air data for the entire time period of EMI’s production to more accurately estimate the CEI for the Marietta residents. Nevertheless, air dispersion modeling was performed by U.S. EPA using the available data and industry-accepted assumptions. It enabled the investigators to obtain proxy Mn-Air concentrations at 1935 receptor sites within the vicinity of the facility. Individual Mn-Air exposure and CEI were generated while protecting the identities of the participants.

By determining biomarkers in blood or serum, the present study could rule out potential confounding by other neurotoxic metals (whole blood: Hg, Pb and Cd) or effect modifying factors such as serum ferritin and hepatic enzymes, which may display a compromised regulation of the systemic Mn status. The good results of mental effort warranted the interpretation that the participants responded reliably and consistently. Hence, generalized anxiety, as measured by the psychometrically constructed and well-validated SCL-90-R, is considered a cardinal sign and result in this study. The quantitative actuarial method of norming and standardized scoring of the SCL-90-R leads to its high incremental validity, which is more effective for use in research than the qualitative interpretation of self-reporting questionnaires.

We performed an epidemiological study with appropriate and strict inclusion/exclusion criteria with adult residents living more than 10 years in a Mn-exposed town. In terms of generalization of these results, as in any community study, we could not control which subjects would return the response card. The initial potential participant list was a random sample; however, the return sample may not be a random sample of the selected sample that were mailed invitations to participate. We could not assess this issue because data were not collected from nonparticipants. However, demographically, the originally randomly selected study sample was similar to the overall census data of the town, and the two towns were demographically similar. This implies that selection bias may not be an issue in our inference of the study results.

Conclusions

The comparison of two Ohio towns for potential exposure to and health effects of airborne Mn found that MnB, questionnaire, neurological assessment and neuropsychological test results did not differ between towns. In Marietta residents, generalized anxiety was higher than in those of Mount Vernon and they also scored lower on some UPDRS tests. Thus, proximity to Eramet affected exposure to airborne Mn, as well as mood/anxiety and performance on motor/movement tests. Whether generalized anxiety and differences on motor/movement are a direct effect of exposure to airborne Mn or are due to generalized anxiety from fear of Mn in air remains unclear.

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Conflict of interest

All authors declare that there are no conflicts of interest.

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